IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	:	10/517,518
Applicant	:	Stefan SPERL
Filed	:	July 1, 2005
TC/A.U.	:	1621
Examiner	:	S. KUMAR
Docket No.	:	2923-671
Customer No.	:	6449
Confirmation No.	:	1246

RESPONSE

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This is in response to the final Action mailed March 8, 2007, and is accompanied by a Request for Continued Examination and a request for a one-month extension of time.

35 USC §103

Reconsideration and withdrawal of the rejection of claims 1-18 under 35 USC §103 as being unpatentable over the combination of WO 92/08709 and WO 00/17158 are respectfully requested.

With respect to claims 1-13, those claims recite methods for the treatment or prevention of urokinase-associated or urokinase receptor-associated diseases via the administration of certain 3-guanidino phenylalanine derivatives. As the Action acknowledges, the compounds of WO '709 are taught to prevent blood coagulation or thrombosis, and there is apparently no teaching or suggestion in WO '709 that the compounds would be useful for the presently claimed purposes. The Action relies on WO

'158 as allegedly providing that suggestion, but it is respectfully submitted the one of ordinary skill would not be so led by that reference.

The compounds disclosed in WO '158 are quite different from the compounds recited in present claims 1-13. The WO '158 compounds are all amidino compounds (*i.e.*, they all have the $C(NH)(NH_2)$ substituent on the phenyl ring), whereas the presently claimed compounds are all guanidino compounds having the $NH\text{-}C(NH)NH_2$ substituent on the phenyl ring. Even with WO '158 in hand, one of ordinary skill would not be led to substitute a guanidino group for an amidino group. There is no suggestion from the references that one would expect guanidino compounds to be urokinase inhibitors from the mere fact that amidino compounds are urokinase inhibitors, and both amidino and guanidino compounds inhibit thrombosis. WO '158 suggests many variables in other portions of the molecule, but all of the compounds contain the amidino group, with no suggestion of variation at that point. It is respectfully submitted that it is only in hindsight with the benefit of the present applicant's specification can it be said to be obvious to modify the WO '158 compounds as posited. Moreover, even if there were motivation in the art to make that change, one would still not have the necessary expectation of success after the modification was made. The references relied on do not provide any structure/activity link between amidino and guanidine groups in the context of inhibiting urokinase activity.

Moreover, even if the combination of references made out a *prima facie* case of obviousness (which they do not), compounds according to the present claims exhibit a surprisingly high selectivity for urokinase compared to plasmin and thrombin. The Examiner's attention is respectfully directed to Example 4 of the present application, which shows that the described 3-guanidino compound was highly selective for urokinase (having a K_i of 0.47 μM) as compared to plasmin (3.8 μM) and thrombin (≥12 μM). By way of comparison, the Examiner's attention is also respectfully directed to page 25 of the

Pentapharm Product Catalog 1998 (citation B on the Information Disclosure Statement submitted December 12, 2006). There, it is reported that the Pefabloc® uPA product had the following inhibition constants: uPA: 0.41 μM; plasmin: 1.0 μM; and thrombin: 0.67 μM. That product is described on page 23 as being Nα-(2, 4, 6-triisopropylphenylsulfonyl)-3-amidino-(L) -phenylalanine-4-ethoxycarbonyl piperazide hydrochloride, which is analogous to the Example 4 compound, except that the former contains the 3-amidino group. The amidino compound does not have the same selectivity for urokinase as does the guanidino compound. The other amidino phenylalanine compounds in the catalog likewise failed to show specificity for urokinase (see data for Pefabloc® TH, TH1158, PL, Xa, Tryp and Try1420 products on page 25). In addition, the assignee of the present application has conducted testing as described in Examples 3 and 4 on an additional compound, *i.e.*, Nα-(2, 4, 6-triisopropylphenylsulfonyl)-3-guanidino-(L) -phenylalanine-4-ethylaminocarbonyl piperazide. The results indicate that the compound likewise was highly selective for urokinase (having a K_i of 0.9 μM) as compared to plasmin (4 μM) and thrombin (>25 μM).[1] It is respectfully submitted that one of ordinary skill would find the high selectivity of the guanidino compounds surprising and unexpected.

The rejection is also defective with respect to claims 14-18. Those claims all recite that R^2 comprises a tri-substituted phenyl radical, preferably a 2,4,6-substituted phenyl radical. In contrast, the WO '709 guanidino compounds at R^4 apparently do not disclose or suggest those radicals.

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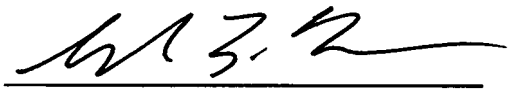
[1] Applicant expects shortly to submit these data in a formal declaration under Rule 132.

Thus, for all of the foregoing reasons, the rejection should not be maintained. It is believed that the present case is in condition for allowance, and a favorable Action is respectfully requested.

Respectfully submitted,



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